Herbal and Dietary Supplement–Induced Liver Injury

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KEYWORDS

• Herbals • Dietary supplements • Liver • Toxicity • Drug-induced liver injury

KEY POINTS

- The increase in the use of herbal and dietary supplements (HDSs) and a growing awareness of the potential for these agent to cause liver injury has been associated with an increase in reports of HDS-associated hepatotoxicity.
- Limited regulatory oversight, inaccurate product labeling, adulterants, and inconsistent sourcing of constituent ingredients may all contribute to the potential for toxicity.
- The spectrum of HDS-induced liver injury is diverse and the outcome may vary from transient liver test abnormalities to acute hepatic failure requiring liver transplantation, or resulting in death.
- The most commonly implicated products include bodybuilding and weight loss products. There are no validated standardized tools to establish the diagnosis, but some HDS products have a clear clinical signature that can make diagnosis almost certain.

INTRODUCTION

Epidemiology

Herbs and botanicals, as well as their metabolites, constituents, and extracts, are included in the definition of dietary supplements in United States federal law.[1] The term herbal and dietary supplements (HDSs) is redundant but commonly used to categorize these products. Although regulated by the US Food and Drug Administration (FDA), dietary supplements are not subject to the safety monitoring and approval process of pharmaceutical drugs.

Disclosure: The authors have nothing to disclose.

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Clin Liver Dis ■ (2016) ■–■
http://dx.doi.org/10.1016/j.cld.2016.08.010 liver.theclinics.com
1089-3261/16/Published by Elsevier Inc.

Despite these agents generally lacking proof of efficacy and their manufacturers not being permitted to make medical claims, these products have gained extremely wide acceptance and their use has increased over recent decades. During this time, the estimated number of supplements marketed in the United States has increased more than 10-fold, from ~4000 in 1993 to ~55,000 in 2012.[2,3] About half of the adult population in the United States reports having used at least 1 dietary supplement in the past month.[4,5] These products are more commonly used by non-Hispanic white people, at older age, and with higher levels of education.[6–9] Most alternative medicine users think that the use of HDS products is consistent with their attitudes toward health and life, and that these agents contribute to their well-being.[10] The use of HDSs is associated with considerable expense. In 2007, $14.8 billion was spent out of pocket on herbal or complementary nutritional products, equivalent to one-third of the out-of-pocket expenditures associated with prescription drug use in the United States.[11]

Nationally, it is estimated that 23,000 emergency department visits each year can be attributed to adverse effects associated with the use of HDSs.[12] Although there have been well-documented outbreaks of acute liver injury associated with specific dietary supplements, the true incidence of HDS-induced liver injury (HILI) is difficult to estimate. In Spain, 2% of investigated cases of drug-induced liver injury have been attributed to HDS,[13] whereas in Iceland the number is approximately 16%.[14] The National Institutes of Health–funded Drug-Induced Liver Injury Network (DILIN) has recently reported that, of total drug-induced liver injury (DILI) cases adjudicated between 2004 and 2013, attribution to HDSs has increased from 7% to 20% (**Fig. 1**).[15] Among patients presenting with acute liver failure, those whose disease was attributed to

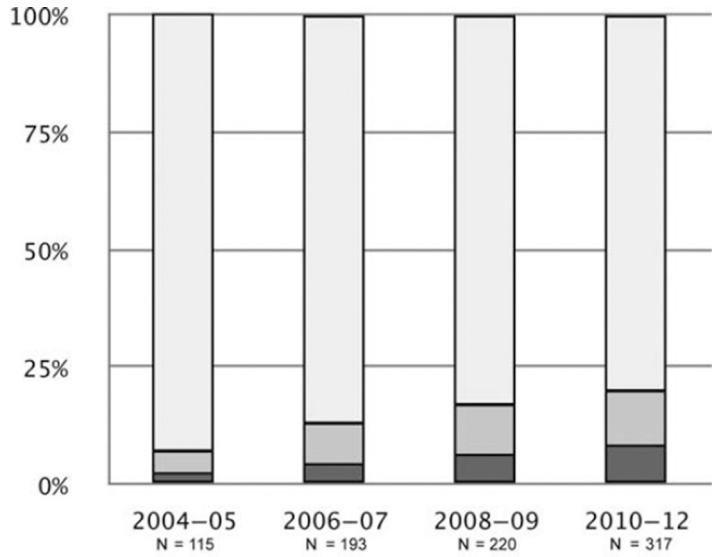

Fig. 1. Increase of the proportion of enrolled patients with DILI caused by HDS products in the DILIN prospective study. Light gray bar represents medications, medium gray bar represents nonbodybuilding HDS, and dark gray bar represents bodybuilding HDS. Trend test for HDS, $P = .0007$; trend test for bodybuilding HDS, $P = .007$; trend test for nonbodybuilding HDS, $P = .05$. (*From* Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. Hepatology 2014;60(4):1403; with permission.)